(FILE 'MEDLINE, EMBASE, CANCERLIT, BIOTECHDS, BIOSIS' ENTERED AT 17:40:17 ON 15 OCT 2003)

		DEL HIS	
L1	21926	S	ANTHRACENE NOT DMBA
L2	216	S	DIMETHYLANTHRACENE
L3	3162930	S	CULTURED OR IN VITRO
L4	1390489	S	CULTURE
L5	3961728	S	L4 OR L3
L6	5161	S	L5 AND L1
L7	899108	S	MUTAGENIC OR MUTAT?
L8	4832	S	HYPERMUTA?
L9	900227	S	L8 OR L7
L10	487	S	L6 AND L9
L11	308	DUP REM	L10 (179 DUPLICATES REMOVED)
L12	6	S	L11 AND L2
L13	375120	S	GENOTOXIC OR TOXIC
L14	43	S	L13 AND L11
L15	93834	S	CARCINOGENIC OR TUMORIGENIC
L16	2263	S	L15 AND L1
L17	606	S	L16 AND L3
L18	25710	S	L15 AND L5
L19	670	S	L16 AND L5
L20	133	S	L19 AND L9
L21	86	DUP REM	L20 (47 DUPLICATES REMOVED)
L22	85	S	L21 NOT 7,12-DIMETHYLBENZ(A)ANTHRACENE

=>

L22 ANSWER 2 OF 85 MEDLINE on STN
AN 1998346713 MEDLINE
DN 98346713 PubMed ID: 9683183
TI Repair of DNA lesions induced by polycyclic aromatic hydrocarbons in human cell-free extracts: involvement of two excision repair mechanisms in **vitro**.
AU Braithwaite E; Wu X; Wang Z
CS Graduate Center for Toxicology, University of Kentucky, Lexington 40536, USA.
NC ES5796 (NIEHS)
SO CARCINOGENESIS, (1998 Jul) 19 (7) 1239-46.
Journal code: 8008055. ISSN: 0143-3334.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199808
ED Entered STN: 19980817
Last Updated on STN: 19980817
Entered Medline: 19980806
AB Polycyclic aromatic hydrocarbons (PAHs) are significant environmental pollutants representing an important risk factor in human cancers. DNA adducts formed by the ultimate carcinogens of PAHs are potentially toxic, **mutagenic** and **carcinogenic**. DNA repair represents an important defense system against these genotoxic insults. Using a human cell-free system we have examined repair of DNA lesions induced by several PAH dihydrodiol epoxides, including anti-(+/-)-benzo[a]pyrene-trans-7,8-dihydrodiol-9,10-epoxide, anti-(+/-)-benz[a]**anthracene** -trans-3,4-dihydrodiol-1,2-epoxide, anti-(+/-)-benz[a]**anthracene** -trans-8,9-dihydrodiol-10,11-epoxide, anti-(+/-)-benzo[b]fluoranthene-trans-9,10-dihydrodiol-11,12-epoxide and anti-(+/-)-chrysene-trans-1,2-dihydrodiol-3,4-epoxide. Effective repair of DNA damage induced by these five PAH metabolites was detected. Two distinct mechanisms of excision repair were observed. The major repair mechanism is nucleotide excision repair (NER). The other mechanism is independent of NER and correlated with the presence of apurinic/apyrimidinic sites in the damaged DNA, thus presumably reflecting base excision repair (BER). However, the contribution of BER to different PAH lesions varied in **vitro**. These results suggest the possibility that BER may also play an important role in repair of certain PAH-induced DNA lesions.

L22 ANSWER 53 OF 85 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 78350492 EMBASE
DN 1978350492
TI Carcinogenicity and mutagenicity of benz(a)**anthracene** diols and diol-epoxides.
AU Slaga T.J.; Huberman E.; Selkirk J.K.; et al.
CS Biol. Div., Oak Ridge Nat. Lab., Oak Ridge, Tenn. 37820, United States
SO Cancer Research, (1978) 38/6 (1699-1704).
CODEN: CNREA8
CY United States
DT Journal
FS 037 Drug Literature Index
016 Cancer
LA English
AB Benz(a)**anthracene** (BA) and its five possible trans-dihydrodiols were evaluated for determination of their skin tumor-initiating activity and their **mutagenic** activity in Chinese hamster V79 cells. In addition, the skin tumor-initiating abilities of five diol-epoxides of BA were tested. Results showed (.+-.)-trans-3,4-dihydroxy-3,4-dihydrobenz-(a)**anthracene** (BA 3,4-dihydrodiol) to be approximately 10 times more **mutagenic** than was BA and about 20 times more **mutagenic** than were the other possible dihydrodiols in the V79 cells cocultivated with irradiated hamster embryo cells. As a skin tumor initiator, BA 3,4-dihydrodiol was approximately 5 times more active than BA, whereas the other BA dihydrodiols were all less active tumor initiators. (.+-.)-trans-3.alpha.,4.beta.-Dihydroxy-1.alpha.,2.alpha.-epoxy-1,2,3,4-tetrahydrobenz(a)**anthracene** was found to be approximately 20% more active as a tumor initiator than was BA 3,4-dihydrodiol, whereas the other diol-epoxides of BA were less active than BA itself. The results suggest that the bay-region diol-epoxide of BA may be the ultimate **carcinogenic** and **mutagenic** form of BA.

L22 ANSWER 64 OF 85 CANCERLIT on STN
AN 91669165 CANCERLIT
DN 91669165
TI METABOLIC ACTIVATION OF HYDROXYMETHYL POLYCYCLIC AROMATIC HYDROCARBONS: ELECTROPHILIC AND **MUTAGENIC** SULFURIC ACID ESTER FORMATION, DNA ADDUCTS, AND CARCINOGENICITY.
AU Surh Y
CS Univ. of Wisconsin, Madison.
SO Diss Abstr Int [B], (1990) 51 (4) 1725.
ISSN: 0419-4217.
DT (THESIS)
LA English
FS Institute for Cell and Developmental Biology
EM 199103
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB Hydroxylation of meso-methyl groups with subsequent formation of reactive benzylic esters bearing good leaving groups such as sulfate, phosphate, and acetate has been proposed as a possible biochemical mechanism of activation and carcinogenicity of methyl-substituted polycyclic aromatic hydrocarbons (PAHs). In support of this postulation, data on the formation of electrophilic and **mutagenic** sulfuric acid esters of several hydroxymethyl PAHs in **vitro** by rat hepatic sulfotransferase activity have been reported. In order to determine the role of the reactive benzylic sulfuric acid ester metabolites in carcinogenesis by parent hydrocarbons, formation of benzylic DNA adducts in the livers of rats or mice treated with 7-hydroxymethyl-12-methylbenz(a) **anthracene** (HMBA), 6-hydroxymethylbenzo(a)pyrene (HMBP), 9-hydroxymethyl-10-methyl-**anthracene** (HMA), and 1-hydroxymethylpyrene (HMP) was investigated. All of these hydroxymethyl hydrocarbons formed benzylic DNA adducts in rat liver in vivo as well as in **vitro** by hepatic cytosols fortified with the sulfo-group donor 3'-phosphoadenosine-5'-phosphosulfate. Dehydroepiandrosterone (DHEA), a typical substrate for hydroxysteroid sulfotransferases, strongly inhibited the rat hepatic cytosolic sulfotransferase activities for HMBA, HMBP, HMA, and HMP. DHEA pretreatment also lowered the levels of hepatic benzylic DNA adducts produced by i.p. injections of these hydrocarbons into infant rats. The electrophilic sulfuric acid esters 7-sulfooxymethyl-12-methylbenz(a)**anthracene** (SMBA), 6-sulfooxymethylbenzo(a)pyrene (SMBP), 9-sulfooxymethyl-10-methylanthracene (SMA), and 1-sulfooxymethylpyrene (SMP) yielded much higher amounts of benzylic DNA adducts in rat liver than did their parent hydroxymethyl hydrocarbons. These reactive esters were also directly **mutagenic** in Salmonella typhimurium TA98 and their intrinsic mutagenicities were significantly reduced by glutathione and glutathione-S-transferase activity. The carcinogenicity of SMBA as determined by several animal tumor models was low and no higher than that of HMBA. The sulfuric acid esters of HMA and HMP were weak skin tumor initiators in mice, but they were more active than the parent hydroxymethyl hydrocarbons in this regard. In contrast, SMBP was much more **carcinogenic** than HMBP and benzo(a)pyrene. (Full text available from University Microfilms International, Ann Arbor, MI, as Order No. AAD90-25733)

L22 ANSWER 76 OF 85 CANCERLIT on STN
AN 77704838 CANCERLIT
DN 77704838
TI LIVER HOMOGENATE-MEDIATED MUTAGENESIS IN CHINESE HAMSTER V79 CELLS BY POLYCYCLIC AROMATIC HYDROCARBONS AND AFLATOXINS.
AU Krahn D F; Heidelberger C
CS McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706.
SO Mutat Res, (1977) 46 (1) 27-44.
ISSN: 0027-5107.
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Assessment Review Committee
EM 197708
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB A mammalian cell **culture** mutagenesis assay using Chinese hamster V79 cells, which are sensitive to the cytotoxic and **mutagenic** effects of several chemical carcinogens that require metabolic activation, is described. The induced frequency of 6-thioguanine-resistant colonies was used to measure **mutagenic** activity. The 9000-g supernatant fraction of rat liver plus cofactors provided the metabolic activation. Eventually, the assay could be utilized to prescreen environmental chemicals. The following chemical carcinogens were examined: aflatoxin B1, aflatoxin B2, benzo(a)pyrene, 3-methylcholanthrene, 7,12-dimethylbenz(a) **anthracene**, dibenz(a,h)-**anthracene**, dibenz(a,c) **anthracene**, and benz(a)**anthracene**. Except for dibenz(a,h)-**anthracene** and dibenz(a,c)**anthracene**, the **mutagenic** activity generally paralleled the **carcinogenic** activity. (64 Refs)

L22 ANSWER 79 OF 85 CANCERLIT on STN
AN 73701234 CANCERLIT
DN 73701234
TI THE INDUCTION OF AZAGUANINE-RESISTANT MUTANTS IN **CULTURED** CHINESE HAMSTER CELLS BY REACTIVE DERIVATIVES OF **CARCINOGENIC** HYDROCARBONS.
AU Duncan M E; Brookes P
CS Chem. Carcinogenesis Div., Chester Beatty Res. Inst., London, England.
SO Mutat Res, (1973) 21 (2) 107-118.
ISSN: 0027-5107.
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Assessment Review Committee
EM 197512
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB 7-Bromdethylbenz(a)**anthracene** (7-BrMeBA), a weak carcinogen, and 7-bromomethyl-12-methylbenz[a]**anthracene** (7-BrMe12MeBA), an active carcinogen, were tested for their abilities to induce azaguanine-resistant mutants in azaguanine-sensitive V79 Chinese hamster cell cultures. Sensitive cells grown for 15 min in medium containing one of the carcinogens were recultured and azaguanine was added at different times. The induced **mutation** frequency increased arithmetically with the number of cell divisions which occurred following exposure to carcinogen and prior to addition of azaguanine, and reached a maximum after three or four divisions. The percentage of induced **mutations** declined sharply when cells were allowed to progress beyond four divisions. At a given concentration, 3H-labeled 7-BrMeBa, the weaker carcinogen, bound five times more extensively to cellular DNA and RNA than did 7-BrMe12BA. At low doses both compounds gave a similar linear **mutation** response with a slope of about 5 x 10-5 induced mutants/ survivor/micromole hydrocarbon bound/mole of DNA phosphorus. However, at extents of DNA binding greater than 8micromoles mole phosphorus, 7-BrMeBA was much more **mutagenic** than 7-BrMe12BA. These data were consistent with the existence of two distinct mechanisms for the induction of mutants by these two hydrocarbon derivatives.

L22 ANSWER 18 OF 85 MEDLINE on STN
AN 79215399 MEDLINE
DN 79215399 PubMed ID: 110710
TI Cell-mediated mutagenesis in **cultured** Chinese hamster cells by polycyclic hydrocarbons: mutagenicity and DNA reaction related to carcinogenicity in a series of compounds.
AU Wigley C B; Newbold R F; Amos J; Brookes P
SO INTERNATIONAL JOURNAL OF CANCER, (1979 May 15) 23 (5) 691-6. Journal code: 0042124. ISSN: 0020-7136.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197909
ED Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19790917
AB Three polycyclic hydrocarbons, benz(a)**anthracene**, 3-methylcholanthrene and 7,12-dimethylbenz(a)**anthracene**, have been studied in a cell-mediated mutagenesis system using BHK 21 cells to metabolize the hydrocarbons and V-79 cells as targets for detecting induced cytotoxicity and **mutation**. In large-scale experiments, the DNA of V-79 cells was analyzed by column chromatography to determine the nature and true extent of reaction of hydrocarbons with dexoyribonucleosides. Products with DNA formed by the two **carcinogenic** compounds were qualitatively very similar to those reported to occur in vivo and in primary cell cultures. Binding indices were calculated from the tritium content of DNA-hydrocarbon products, related to overall metabolism, for these two compounds together with benzo(a)pyrene and 7-methylbenz(a)**anthracene** using data from a previous study. These values reflected differences in **carcinogenic** potency between the compounds. Induced **mutation** frequencies were related to the extent of DNA reaction with each compound. At equivalent extents of DNA reaction with hydrocarbon products, levels of induced **mutation** were not significantly different.

L22 ANSWER 12 OF 85 MEDLINE on STN
AN 83062605 MEDLINE
DN 83062605 PubMed ID: 7144778
TI Sister-chromatid exchange and chromosomal aberration induction in **cultured** Chinese hamster cells by the monomethylbenz[a]anthracenes.
AU Connell J R
SO MUTATION RESEARCH, (1982 Sep) 102 (2) 173-82.
Journal code: 0400763. ISSN: 0027-5107.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198301
ED Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19830107
AB The ability of the 12 monomethylbenz[a]**anthracene** isomers, following their metabolism by using the cell-mediated activation system, to induce 8-azaguanine-resistant mutants, sister-chromatid exchanges (SCEs) and chromosomal aberrations has been measured. Both the **mutagenic** potency and the ability of the monomethylbenz[a]anthracenes to induce SCEs correlated with their **carcinogenic** activity. None of the monomethylbenz[a]anthracenes were particularly clastogenic.

L12 ANSWER 6 OF 6 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 2003-12425 BIOTECHDS
TI Generating antibiotic resistant bacteria, by blocking mismatch repair in bacterium, contacting the bacterium with an antibiotic, selecting the bacterium that is resistant to the antibiotic, and culturing the bacterium;
plasmid-mediated antisense gene transfer for antibiotic-resistance bacterium construction using DNA microarray for use in genomics
AU NICOLAIDES N C; SASS P M; GRASSO L; KLINE J B
PA MORPHOTEK INC
PI WO 2003012130 13 Feb 2003
AI WO 2001-US23888 25 Jul 2001
PRAI WO 2001-23888 25 Jul 2001; WO 2001-23888 25 Jul 2001
DT Patent
LA English
OS WPI: 2003-278404 [27]
AB DERWENT ABSTRACT:
NOVELTY - Generating (M1) or producing antibiotic resistant bacteria, involves blocking mismatch repair or overexpressing a mismatch repair gene in a bacterium or culturing bacteria with a natural defect in mismatch repair, contacting the bacterium with an antibiotic, selecting the bacterium that is resistant to the antibiotic or determining if the bacterium is resistant to the antibiotic, and culturing the bacterium.

DETAILED DESCRIPTION - Generating (M1) or producing antibiotic resistant bacteria, involves blocking mismatch repair or overexpressing a mismatch repair gene in a bacterium or culturing bacteria with a natural defect in mismatch repair, contacting the bacterium with an antibiotic, selecting the bacterium that is resistant to the antibiotic or determining if the bacterium is resistant to the antibiotic, and culturing the bacterium. M1 further comprises blocking mismatch repair in a bacterium, where the bacterium becomes **hypermutable**, contacting the bacterium with at least one antibiotic, selecting the bacterium that is resistant to the antibiotic, and culturing the bacterium INDEPENDENT CLAIMS are also included for the following: (1) identifying (M2) a mutant gene conferring antibiotic resistance, by comparing the genome of antibiotic resistant bacterium made by M1 to the genome of a wild-type strain of the bacterium; and (2) an antibiotic resistant bacterium (I) produced by M1.

WIDER DISCLOSURE - Also disclosed as new is a pharmaceutical composition comprising an antimicrobial agent targeted against certain antibiotic resistant strains.

BIOTECHNOLOGY - Preferred Method: In M1, the mismatch repair is blocked by introducing a dominant negative allele of a mismatch repair gene into the bacterium. The dominant negative allele of a mismatch repair gene is a PMS2-134 gene. The mismatch repair is blocked by introducing an antisense nucleic acid molecule into the bacterium, where the antisense nucleic acid molecule specifically binds to a mismatch repair gene and inhibits mismatch repair. The compound is **anthracene** substituted by 1-10 of H, hydroxyl, amino, alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, alkyl sulfonate, CN, NO2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups, where heteroalkyl, heteroaryl, and substituted heteroaryl contains at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen, where substituents of the substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and

substituted heteroaryl are halogen, CN, NO2, lower alkyl, aryl, heteroaryl, aralkyl, aralkyloxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino, and where the amino groups are optionally substituted with an acyl group, or 1-3 aryl or lower alkyl groups. The compound is preferably 1,2-**dimethylanthracene**, 9,10-dimethyl **anthracene**, 7,8-**dimethylanthracene**, 9,10-diphenylanthracene, 9,10-dihydroxymethylanthracene, 9-hydroxymethyl-10-methylanthracene, **dimethylanthracene** -1,2-diol, 9-hydroxymethyl-10-methylanthracene-1,2-diol, 9-hydroxymethyl-10-methylanthracene-3,4-diol, 9,10-di-m-tolyanthracene. M1 further comprises exposing the bacterium to a chemical mutagen selected from methane sulfonate, dimethyl sulfonate, O-6-methyl benzadine, ethylnitrosourea, ethidium bromide, ethyl methanesulfonate, N-methyl-N'-nitro-N-nitrosoguanidine, methylnitrosourea, Tamoxifen, and 8-hydroxyguanine. The compound is selected from an ATP analog (such as AMP-PNP or ATP(gamma)S), a nuclease inhibitor (such as N-ethylmaleimide, heterodimeric adenine-chain-acridine compounds, exonuclease III inhibitors or heliquinomycin), and a DNA polymerase inhibitor (such as actinomycin D analogs, aphidicolin, 1-(2'-Deoxy-2'-fluoro-beta-L-arabinofuranosyl)-5-methyluracil, and 2',3'-dideoxyribonucleoside 5'-triphosphates. M1 further involves determining whether the bacterium is resistant to the antibiotic by analyzing the bacterium for multiantibiotic resistance, and making antibiotic resistant bacteria genetically stable by removing the mismatch repair (MMR) inhibitory molecule. In M2, the genome of the antibiotic resistant bacterium and the genome of the wild-type strain of the bacterium are compared by sequence analysis of the entire genome or microarray analysis. The genome of the antibiotic resistant bacterium and the genome of the wild type strain of the bacterium are compared by introducing gene fragments from the antibiotic resistant bacterium into the wild type bacterium, thereby producing mutant bacteria, selecting a mutant bacterium with antibiotic resistance, and sequencing the gene fragment from the mutant bacterium with antibiotic resistance, or by introducing gene fragments from the wild-type strain of the bacterium into the antibiotic resistant strain of the bacterium, selecting a mutant bacterium with antibiotic resistance, and sequencing the gene fragment from the mutant bacterium.

USE - M1 is useful for generating or producing antibiotic resistant bacteria that are resistant to an antibiotic such as quinilone, aminoglycoside, magainin, defensin, tetracycline, beta-lactum, macrolide, lincosamide, sulfonamide, chloramphenicol, nitrofurantoin, or isoniazid (claimed). M1 is useful for identifying, characterizing and evaluating targets for therapeutic development. (I) is also useful for gene/protein discovery to identify new biomolecules that are involved in generating resistance, and to screen for antimicrobial agents targeted against certain antibiotic resistant strains. The antimicrobial agents are used for treating microbial infections in mammals.

EXAMPLE - Generation of antibiotic resistant bacteria was as follows: To demonstrate the ability to produce antibiotic resistant bacterial strains by inhibiting mismatch repair (MMR), 107 bacterial cells expressing either the vector (pT7Ea) or pT7PMS134/V5 were inoculated into 5 ml LB broth plus the appropriate antibiotic concentrations such as 4.70 microg/ml of tetracycline, 7.10 microg/ml of nalidixic acid, 0.13 microg/ml of ofloxacin, 0.13% of norfloxacin and 250.0 microg/ml of vancomycin and grown overnight at 37degreesC with shaking. Antibiotic concentrations were based on the minimum inhibitory concentrations (MIC) observed to inhibit the growth of bacteria constitutively expressing the mar operon. Titration analysis found the following amounts to be effective in inhibiting bacterial growth in the presence of various compounds. The next day, cultures were analyzed for cell growth in the presence or absence of antibiotics. No growth was observed in bacterial control cells (pT7Ea), which had OD levels similar to blank **culture**. In contrast, significant **culture** growth was observed in pT7PMS134V5 and pT7PMSR3 cultures grown in all antibiotics tested. To test the stability resistance, cells were replated

and followed for growth in the presence of 1X MIC concentration of antibiotic. Bacterial cells were inoculated at 1x107 cells/ml and grown for 6 hours in the presence of tetracycline (Tet). pT7Ea control **culture** did not grow in the presence of Tet while pT7PMS134 and pT7PMSR3 cultures resistant to Tet grew to confluence at time 4 hours after inoculation. These data demonstrated the ability to generate antibiotic resistant cultures by blocking MMR and re-establishing genetically stable cultures that can be used for gene discovery. (127 pages)

L14 ANSWER 1 OF 43 MEDLINE on STN
AN 2001483091 MEDLINE
DN 21417574 PubMed ID: 11525907
TI Aryl hydrocarbon receptor-mediated activity of **mutagenic** polycyclic aromatic hydrocarbons determined using in **vitro** reporter gene assay.
AU Machala M; Vondracek J; Blaha L; Ciganek M; Neca J V
CS Veterinary Research Institute, 62132, Brno, Czech Republic.. machala@vri.cz
SO MUTATION RESEARCH, (2001 Oct 18) 497 (1-2) 49-62. Journal code: 0400763. ISSN: 0027-5107.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20010830
Last Updated on STN: 20020122
Entered Medline: 20011218
AB Activation of aryl hydrocarbon receptor (AhR) by 30 polycyclic aromatic hydrocarbons (PAHs) was determined in the chemical-activated luciferase expression (CALUX) assay, using two exposure times (6 and 24h), in order to reflect the metabolization of PAHs. AhR-inducing potencies of PAHs were expressed as induction equivalency factors (IEFs) relative to benzo[a]pyrene and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In 24h exposure assay, the highest IEFs were found for benzo[k]fluoranthene, dibenzo[a,h]**anthracene** and dibenzo[a,k]fluoranthene (approximately three orders of magnitude lower than TCDD) followed by dibenzo[a,j]**anthracene**, benzo[j]fluoranthene, indeno[1,2,3-cd]pyrene, and naphtho[2,3-a]pyrene. The 6h exposure to PAHs led to a significantly higher AhR-mediated activity than the 24h exposure (generally by two orders of magnitude), probably due to the high rate of PAH metabolism. The strongest AhR inducers showed IEFs approaching that of TCDD. Several PAHs, including some strong mutagens, such as dibenzo[a,l]pyrene, cyclopenta[cd]pyrene, and benzo[a]perylene, elicited only partial agonist activity. Calculation of IEFs based on EC25 values and/or 6h exposure data is suggested as an alternative approach to estimation of **toxic** potencies of PAHs with high metabolic rates and/or the weak AhR agonists. The IEFs, together with the recently reported relative **mutagenic** potencies of PAHs [**Mutat**. Res. 371 (1996) 123; **Mutat**. Res. 446 (1999) 1] were combined with data on concentrations of PAHs in extracts of model environmental samples (river sediments) to calculate AhR-mediated induction equivalents and **mutagenic** equivalents. The highest AhR-mediated induction equivalents were found for benzo[k]fluoranthene and benzo[j]fluoranthene, followed by indeno[1,2,3-cd]pyrene, dibenzo[a,h]**anthracene**, benzo[a]pyrene, dibenzo[a,j]**anthracene**, chrysene, and benzo[b]fluoranthene. High **mutagenic** equivalents in the river sediments were found for benzo[a]pyrene, dibenzo[a,e]pyrene, and naphtho[2,3-a]pyrene and to a lesser extent also for benzo[a]**anthracene**, benzo[b]fluoranthene, indeno[1,2,3-cd]pyrene, benzo[j]fluoranthene, dibenzo[a,e]fluoranthene and dibenzo[a,i]pyrene. These data illustrate that AhR-mediated activity of PAHs, including the highly **mutagenic** compounds, occurring in the environment but not routinely monitored, could significantly contribute to their adverse effects.

L14 ANSWER 11 OF 43 MEDLINE on STN
AN 85163568 MEDLINE
DN 85163568 PubMed ID: 3920514
TI Genotoxicity studies with mineral oils; effects of oils on the microbial mutagenicity of precursor mutagens and **genotoxic** metabolites.
AU Watson W P; Brooks T M; Gonzalez L P; Wright A S
SO MUTATION RESEARCH, (1985 Apr) 149 (2) 159-70.
Journal code: 0400763. ISSN: 0027-5107.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198505
ED Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850502
AB In **vitro** genotoxicity assays are extensively used to predict carcinogenic activity in vivo. The standard microbial mutagenicity assays however often fail to yield positive results with mineral oils which are carcinogenic to mice in long-term skin-cancer studies. A comprehensive programme of studies has therefore investigated the basis of this apparently anomalous behaviour. This investigation has addressed the possible effects of oils on the bioactivation of precursor mutagens and the disposition of **mutagenic** metabolites by studying the microbial mutagenicity of selected precursor mutagens (benzo[a]pyrene, benzo[a]**anthracene**, 2-aminoanthracene and 2-naphthylamine) and intrinsically reactive mutagens [+/-)-benzo[a]pyrene-4,5-oxide and (+/-)-7 beta,8 alpha-dihydroxy-9 alpha,10 alpha-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene) in the presence and absence of mineral oils. Notably the mutagenicity associated with the deliberate additions of these mutagens or precursor mutagens to oils was readily detected by the microbial assays. The mutagenicity of only one of the precursor mutagens, benzo[a]pyrene, was significantly reduced by the oils, and then only in the standard plate-incorporation assay. Interestingly the degree of suppression appeared to be related to the polycyclic aromatic hydrocarbon content of the oils. In the case of 2-aminoanthracene large enhancements in its mutagenicity were observed in the presence of oils. These latter findings appear to be due to effects of oils on the bioactivation of precursor mutagens rather than on the disposition of their bioactivation products. The mutagenicity of intrinsically reactive mutagens, of a type generated by bioactivation of polycyclic aromatic hydrocarbons, was not significantly reduced in the presence of mineral oils. This indicates that it is unlikely that components in oils trap or facilitate the deactivation of ultimate mutagens whether these pre-exist in the oil or are formed from precursors by bioactivation in the in **vitro** test system. Viewed overall these results suggest that mineral oils judged to be carcinogenic on the basis of in vivo studies in mouse skin may possess only very weak **genotoxic** potential. While this potential is likely to be a prerequisite for carcinogenic action, the current results cause attention to be focussed on other factors, e.g. promotion, as potentially important determinants of the carcinogenic potencies of mineral oils in mouse skin.

L14 ANSWER 6 OF 43 MEDLINE on STN
AN 1998346713 MEDLINE
DN 98346713 PubMed ID: 9683183
TI Repair of DNA lesions induced by polycyclic aromatic hydrocarbons in human cell-free extracts: involvement of two excision repair mechanisms in **vitro**.
AU Braithwaite E; Wu X; Wang Z
CS Graduate Center for Toxicology, University of Kentucky, Lexington 40536, USA.
NC ES5796 (NIEHS)
SO CARCINOGENESIS, (1998 Jul) 19 (7) 1239-46.
Journal code: 8008055. ISSN: 0143-3334.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199808
ED Entered STN: 19980817
Last Updated on STN: 19980817
Entered Medline: 19980806
AB Polycyclic aromatic hydrocarbons (PAHs) are significant environmental pollutants representing an important risk factor in human cancers. DNA adducts formed by the ultimate carcinogens of PAHs are potentially **toxic**, **mutagenic** and carcinogenic. DNA repair represents an important defense system against these **genotoxic** insults. Using a human cell-free system we have examined repair of DNA lesions induced by several PAH dihydrodiol epoxides, including anti-(+/-)-benzo[a]pyrene-trans-7,8-dihydrodiol-9,10-epoxide, anti-(+/-)-benz[a]**anthracene**-trans-3,4-dihydrodiol-1,2-epoxide, anti-(+/-)-benz[a]**anthracene**-trans-8,9-dihydrodiol-10,11-epoxide, anti-(+/-)-benzo[b]fluoranthene-trans-9,10-dihydrodiol-11,12-epoxide and anti-(+/-)-chrysene-trans-1,2-dihydrodiol-3,4-epoxide. Effective repair of DNA damage induced by these five PAH metabolites was detected. Two distinct mechanisms of excision repair were observed. The major repair mechanism is nucleotide excision repair (NER). The other mechanism is independent of NER and correlated with the presence of apurinic/apyrimidinic sites in the damaged DNA, thus presumably reflecting base excision repair (BER). However, the contribution of BER to different PAH lesions varied in **vitro**. These results suggest the possibility that BER may also play an important role in repair of certain PAH-induced DNA lesions.

N 1984002447
TI Bovine bladder urothelial cell activation of carcinogens to metabolites **mutagenic** to Chinese hamster V79 cells and Salmonella typhimurium.
AU Oglesby L.A.; Hix C.; Snow L.; et al.
CS Northrop Services Inc., Research Triangle Park, NC, United States
SO Cancer Research, (1983) 43/11 (5194-5199).
CODEN: CNREA8
CY United States
DT Journal
FS 037 Drug Literature Index
016 Cancer
028 Urology and Nephrology
004 Microbiology
052 Toxicology
LA English
AB The ability of bovine bladder urothelial cells to activate **genotoxic** chemicals to mutagens was examined by cocultivating bladder cells with Chinese hamster V79 cells or Salmonella typhimurium as mutable targets. Activation of test chemicals to **mutagenic** intermediates by urothelial cells was detected by induction of 6-thioguanine resistance in V79 cells or by induction of histidine revertants in Salmonella. In the bladder cell-mediated V79 cell mutagenesis system, a significant increase in **mutation** frequency was induced by exposure to 7,12-dimethylbenz(a)**anthracene** and dimethylnitrosamine. The aromatic amines 2-aminofluorene, 2-acetylaminofluorene, and 4-aminobiphenyl were weakly **mutagenic** to V79 cells with bladder cell activation, while no **mutagenic** activity was detected with 1-naphthylamine, 2-naphthylamine, or benzidine. Because the **mutagenic** activity of the aromatic amines was low with V79 cells as the target, a bladder cell-mediated S. typhimurium system was developed for these chemicals. The aromatic amines 2-aminofluorene, 2-acetylaminofluorene, 4-aminobiphenyl and 2-naphthylamine were **mutagenic** to S. typhimurium TA98 and TA100 in the presence of bladder cells but not in their absence. Benzidine was **mutagenic** to TA98 but not to TA100. The putative noncarcinogen 1-naphthylamine was not **mutagenic** in the system. In contrast to the V79 data, 7,12-dimethylbenz(a)**anthracene** and dimethylnitrosamine were not **mutagenic** with either bacterial strain. **Mutagenic** responses were related to both the number of bladder cells used for activation and the concentration of test chemical in the Salmonella assay. The data demonstrate that bovine bladder urothelial cells can activate carcinogens from three chemical classes to mutagens and indicate the different sensitivites of V79 cells and S. typhimurium to **genotoxic** agents.

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AN 2001100910 EMBASE

TI Formation of DNA adducts from oil-derived products analyzed by (32)P-HPLC.

AU Akkineni L.K.; Zeisig M.; Baranczewski P.; Ekstrom L.-G.; Moller L.

CS L. Moller, Karolinska Institutet, Department of Biosciences, Unit for Analytical Toxicology, 141 57 Huddinge, Stockholm, Sweden. lennart.moller@cnt.ki.se

SO Archives of Toxicology, (2000) 74/11 (720-731).
Refs: 45
ISSN: 0340-5761 CODEN: ARTODN

CY Germany

DT Journal; Article

FS 052 Toxicology

LA English

SL English

AB The aim of this study was to investigate the genotoxic potential of DNA adducts and to compare DNA adduct levels and patterns in petroleum vacuum distillates, coal tar distillate, bitumen fume condensates, and related substances that have a wide range of boiling temperatures. An in **vitro** assay was used for DNA adduct analysis with human and rat S-9 liver extract metabolic activation followed by (32)P-postlabeling and (32)P-high-performance liquid chromatography ((32)P-HPLC). For petroleum distillates originating from one crude oil there was a correlation between in **vitro** DNA adduct formation and **mutagenic** index, which showed an increase with a distillation temperature of 250.degree.C and a peak around a distillation point of approximately 400.degree.C. At higher temperatures, the genotoxicity (DNA adducts and mutagenicity) rapidly declined to very low levels. Different petroleum products showed a more than 100-fold range in DNA adduct formation, with severely hydrotreated base oil and bitumen fume condensates being lowest. Coal tar distillates showed ten times higher levels of DNA adduct formation than the most potent petroleum distillate. A clustered DNA adduct pattern was seen over a wide distillation range after metabolic activation with liver extracts of rat or human origin. These clusters were eluted in a region where alkylated aromatic hydrocarbons could be expected. The DNA adduct patterns were similar for base oil and bitumen fume condensates, whereas coal tar distillates had a wider retention time range of the DNA adducts formed. Reference substances were tested in the same in **vitro** assay. Two- and three-ringed nonalkylated aromatics were rather low in genotoxicity, but some of the three- to four-ringed alkylated aromatics were very potent inducers of DNA adducts. Compounds with an amino functional group showed a 270-fold higher level of DNA adduct formation than the same structures with a nitro functional group. The most potent DNA adduct inducers of the 16 substances tested were, in increasing order, 9,10-**dimethylanthracene**, 7,12-dimethylbenz[a]**anthracene** and 9-vinylanthracene. Metabolic activation with human and rat liver extracts gave rise to the same DNA adduct clusters. When bioactivation with material from different human individuals was used, there was a significant correlation between the CYP 1A1 activity and the capacity to form DNA adducts. This pattern was also confirmed using the CYP 1A1 inhibitor ellipticine. The (32)P-HPLC method was shown to be sensitive and reproducible, and it had the capacity to separate DNA adduct-forming substances when applied a great variety of petroleum products.